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Subclinical Hypothyroidism and its Relation to Cardiac Dysfunction

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PERMISSION

Title

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Abstract

Hypothyroidism is a very common condition and can be seen throughout the lifespan. The effects on heart function include decreased contractility, increased peripheral vascular resistance, increased diastolic blood pressure and irregular heart rhythms (ATA, 2020). The case study in this report shows typical symptoms of hypothyroidism and proper treatment. The findings collected in this study suggest it beneficial to treat symptomatic subclinical hypothyroidism with added benefits of preserving cardiac dysfunction. But more studies need to be conducted to ensure the efficacy of treating both asymptomatic and symptomatic subclinical hypothyroidism. Having a better understanding of thyroid function and its impact on the heart will allow healthcare providers to make better clinical decisions when treating hypothyroidism and subsequent cardiac dysfunction. In this study, the focus is on the effects of hypothyroidism and how it plays a role in cardiac function.

Background

Hypothyroidism is an underactive thyroid gland. Hypothyroidism means that the thyroid gland doesn't make enough thyroid hormone to keep the body running normally. Common causes are autoimmune disease, such as Hashimoto's thyroiditis, surgical removal of the thyroid, and radiation treatment (ATA, 2020). When thyroid hormone levels are too low, the body's cells are deprived of circulating free T3 and T4 and the body's metabolic processes start slowing down. Symptoms of hypothyroidism include feeling colder, malaise or tire more easily, dry skin, forgetfulness, depression, and constipation (ATA, 2020). Because the symptoms of hypothyroidism are so variable and nonspecific, the only way to know for sure is with a blood test for thyroid stimulating hormone (TSH). Normal range should be between 0.4-4.0 (ATA, 2020).

Hypothyroidism may not cause noticeable symptoms in the early stages. Over time, untreated hypothyroidism can cause a number of health problems, such as obesity, joint pain, infertility and heart disease. Accurate thyroid function tests are available to diagnose hypothyroidism. The most common cause of hypothyroidism is an autoimmune disorder known as Hashimoto's thyroiditis. Autoimmune disorders occur when your immune system produces antibodies that attack your own tissues. Sometimes this process involves your thyroid gland. The trace mineral iodine found primarily in seafood, seaweed, plants grown in iodine-rich soil and iodized salt is essential for the production of thyroid hormones. Too little iodine can lead to hypothyroidism, and too much iodine can worsen hypothyroidism in people who already have the condition. In some parts of the world, iodine deficiency is common, but the addition of iodine to table salt has virtually eliminated this problem in the United States (Mayo Clinic, 2019).

Hypothyroidism can be further divided into “overt” and “subclinical” hypothyroidism. Hypothyroidism is diagnosed when low levels of the thyroid hormones result in elevated levels of TSH (Udovcic et al, 2017). Subclinical hypothyroidism is defined as a state with high TSH with normal blood levels of T4 and T3 (Udovcic et al, 2017). Subclinical hypothyroidism (SHT) is diagnosed when the above listed is present along with being symptomatic (Udovcic et al, 2017). Although, up to 60% of patients with subclinical hypothyroidism can return to euthyroidism over 5 years, again based on TSH levels and antibody status. (Udovcic et al. 2017).

The major effects of thyroid hormones on the heart are mediated by triiodothyronine (T3). Indeed, T3 generally increases the force and speed of systolic contraction and the speed of diastolic relaxation. In addition, T3 decreases vascular resistance, including coronary vascular tone, and increases coronary arteriolar angiogenesis (Grais & Sowers, 2014). These multiple thyroid hormone effects are largely mediated by the action of nuclear-based thyroid hormone

receptors (TR), specifically the TRα and -β. TRα is the predominant TR isoform in the heart, and it is the predominant subtype through which T3 binds to nuclear TRs and signals in cardiomyocytes (Grais & Sowers, 2014).

Thyroid hormone plays a large role in cardiovascular function. Thyroid hormones can promote both physiological and pathological myocardial hypertrophy. In this regard, cardiac hypertrophy, in its initial phases, presents a physiological process that includes increased adenosine triphosphatase (ATP) and gene expression of the sarcoplasmic reticulum Ca 2+ (SERCa 2+) and decreased expression of MHCβ. T3-activated TR cardiac effects also include the regulation of cation transport (Grais & Sowers, 2014). Regulation of intracellular Ca 2+ ([Ca 2+] I) is important for both normal systolic and diastolic function. For example, T3 promotes increases in SERCa 2+ ATPase and the ryanodine channel, and decreases phosphorylation/activation of phospholamban, which functions to inhibit the SERCa 2+ pump.

Diastolic function of the heart is substantially influenced by the thyroid status. The speed of diastolic relaxation in the heart is markedly influenced by lowering of the [Ca 2+] I levels. In cardiomyocytes, most [Ca 2+] I lowering is achieved by pumping [Ca 2+] I into the sarcoplasmic reticulum by the SERCa 2+ pump. Experimental results in animal models of hypothyroidism indicate that the level and activity of the SERCa 2+ pump is markedly decreased and that of inhibitory phospholamban increased (Grais & Sowers, 2014). These SERCa 2+ and phospholamban changes can be linked to a decrease in the rate of diastolic relaxation. Finally, the β 1 adrenergic and the TRα receptors are positively and negatively regulated by T3, respectively, which promotes optimal modulation of T3-activated TR inotropic and chronotropic cardiac effects (Grais & Sowers, 2014).

Thyroid hormones exert effects on the vasculature that generally lead to reduced vascular tone and maintenance of normal arteriolar remodeling. It has been known for two decades that T3 exerts direct effects on vascular smooth muscle cells to promote relaxation (Grais & Sowers, 2014). Several mechanisms for this T3-mediated vascular relaxation have been reported. For example, it has been demonstrated that T3 dose-dependently reduces expression of the angiotensin (Ang) II type 1 receptor and reduces the increased [Ca 2+] I and contractile response to Ang II (Grais & Sowers, 2014). Further, T3 stimulates nitric oxide (NO) production via activation of the phosphoinositol 3-kinase/protein kinase B-mediated endothelial NO synthase signaling pathway (Grais & Sowers, 2014). The resulting increase in bioavailable NO is associated with decreased myosin light chain phosphorylation in response to Ang II and phenylephrine (Grais & Sowers, 2014). Collectively, these data suggest that T3 reduces vascular smooth muscle cell contraction by decreasing [Ca 2+] I as well as Ca 2+ sensitization (Grais & Sowers, 2014). Grais and Sowers (2014) have shown that T3 also promotes angiogenesis and increases the density of small arterioles, including coronary arterioles. This T3-activated TR effect on coronary arterioles may be especially important following myocardial ischemia and in the process of myocardial ischemic reconditioning (Grais & Sowers, 2014).

Case Report

Subjective: Jane Doe is a 42-year-old female that presents to the clinic with complaints of increased fatigue, weight gain, hair loss and occasional slowed heart rate. At this time, she noticed she was feeling more tired than usual, unable to do the tasks she has come accustomed to without being fatigued. She complains of unusual weight gain without a change in diet or activity. She also noticed more hair falling out in the shower. She denies shortness of breath, nausea/vomiting, abdominal pain, changes in hearing or vision, headaches, muscle aches or

changes in bladder or bowel habits. Patient is not currently on any medications, occasionally takes multivitamin, no iodine supplements. Family history of hyperthyroidism in mother and heart disease in father, died of "heart attack" at age 65.

Objective: labs: TSH: 7.5 T3: wnl T4: 3 ug/dl CBC: wnl BMP: wnl Hcg: negative

Vitals: HR 59, BP 135/89, temp 98.7, RR 16, weight 165 lb, height 5'8"

12-lead ECG: normal sinus rhythm with bradycardia

Assessment: no thyroid nodules palpated, no cervical or tonsillar adenopathy, grade 2 systolic murmur heard over left and right sternal border, S1 and S2 heard. Lung sounds normal, no rhales, wheezes or rhonchi. Nails and hair are brittle, no suspicious moles or lesions. Denies any influenza like symptoms, no changes in hearing or vision, denies headaches, denies syncopal episodes.

Plan: given her elevated TSH and decreased T4 it is likely she has overt hypothyroidism. Patient was started on Levothyroxine 25 mcg oral once daily. She will follow up in 6 weeks. We also discussed fasting at next visit as we will be checking a lipid panel and blood sugar. Given that she is bradycardic, hypertensive and has a family history of heart disease we will follow up with further cardiac testing.

Literature Review

This review will focus on the early recognition and need for treatment in subclinical hypothyroidism as it relates to preserving and correcting suboptimal heart function. The main areas of focus include: pharmacologic therapy, treating subclinical hypothyroidism in patients to

prevent or improve cardiac dysfunction, monitoring and duration of treatment and treating subclinical hypothyroidism as a clinical diagnosis.

Pharmacologic Therapy

Hypothyroidism is typically treated with levothyroxine in order to attain a euthyroid state. Doses typically start at 25mcg oral levothyroxine daily. Grais and Sowers (2014) discussed the slow progression and initial starting dose of levothyroxine as low as 12.5mcg oral daily for those with known CAD and decreased heart function. It's also important to determine if hypothyroidism is caused by autoimmune disorders as this will affect treatment plan for dosing and monitoring.

In a study performed by Jabbar et al (2015) the target TSH was between 0.4 to 2.5 mU/L. Levothyroxine dosing was consistent in both studies with small doses starting at 25mcg daily with the dose being increased every four weeks. Increases were made at 25 mcg increments every four weeks until the serum TSH is within the target range. Safety measures (ECG, symptoms of heart failure, and pulse oximetry) were assessed at visits two and six.

Treating Subclinical Hypothyroidism to Prevent or Improve Cardiac Dysfunction

Thyroid dysfunction is compensated for by the greater stimulation of TSH from the anterior pituitary gland (Grais & Sowers, 2014). Despite normal levels of thyroid hormone(T3,T4), SHT patients are at somewhat increased risk of atherosclerosis (Grais & Sowers, 2014). The clinical decision about starting thyroid supplement therapy will be influenced by the age of the patient, the cause of the hypothyroidism, and the presence of other atherosclerotic risk factors including hypertension and dyslipidemia (Grais & Sowers, 2014).

These risk factors for atherosclerosis require appropriate medical management along with thyroid supplementation (Grais & Sowers, 2014).

Endothelial dysfunction is a known early progenitor of hypertension and atherosclerosis. There is evidence of decreased nitric oxide (NO)-mediated vascular relaxation in patients with subclinical hypothyroidism, as demonstrated by abnormal flow-mediated vasodilatation (Grais & Sowers, 2014). Flow-mediated vasodilatation depends on the presence of adequate bioavailable NO in the endothelium. Evaluation of endothelial-mediated vascular relaxation has revealed reduced flow-mediated vasodilatation in individuals with subclinical hypothyroidism (Grais & Sowers, 2014). Baseline and flow-mediated (NO-dependent) vasodilatation values were significantly higher in individuals with subclinical hypothyroidism after treatment with L-thyroxin. Grais and Sowers (2014) support the notion that thyroid replacement therapy is beneficial in patients with subclinical hypothyroidism. Left and right ventricular systolic and diastolic dysfunction also have been described in subclinical hypothyroidism, and there is evidence for improvement in ventricular function with thyroid replacement therapy (Grais & Sowers, 2014).

Subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and mortality with elevated TSH levels, especially in those with values greater than 10 mIU/L. Udovcic et al (2017) suggested an increased risk of coronary heart disease, cardiovascular mortality and an increased risk of cardiovascular disease in younger individuals with the cut-off age varying from 50 to 70 years. Treatment with levothyroxine in those with overt thyroid dysfunction has been shown to improve LDL cholesterol, total cholesterol, triglycerides, hypertension, diastolic dysfunction, heart rate, and heart rate variability in exercise and to delay progression of atherosclerosis (Udovcic et al, 2017). Patients with cardiomyopathies

may demonstrate improved cardiac contractility and stroke volume with levothyroxine treatment (Udovcic et al, 2017). One of the main concerns with starting levothyroxine replacement is the precipitation of myocardial ischemia or arrhythmias, which, although rare, are known to occur (Udovcic et al, 2017).

In subclinical hypothyroidism patients, increased left ventricular (LV) myocardial proton spin-lattice relaxation time (T1) suggest myocardial injury might occur even when serum FT3 were normal (Liu et al, 2018). SHT could alter collagen, myocardial fiber orientation, tissue water content, and capillary blood flow distribution, however, the mechanism of the elevation of LV myocardial T1 remains unclear. Thyroid hormone correlated with LV myocardial T1, indicating that decreased serum thyroid hormone might associate with the myocardial diffused abnormality and T1 value can be regarded as non-invasive surrogate of mild myocardial injury induced by HT (Liu et al, 2018).

The alterations found in myocardial function, metabolic profile, and vascular function suggest that patients with untreated subclinical hypothyroidism may be at increased risk of adverse cardiovascular outcomes. However, individual-patient meta-analysis performed by the Thyroid Studies Collaboration, a consortium of cohort studies with data from more than 75,000 participants, did not demonstrate an association of subclinical hypothyroidism with increased risk of atrial fibrillation, heart failure, stroke, coronary heart disease events, mortality from coronary heart disease, or overall mortality compared with euthyroid individuals (JAMA, 2019). In contrast, when data were analyzed, stratified by degree of thyrotropin elevation, thyrotropin levels of 10 mU/L or higher were associated with increased risk of heart failure, coronary heart disease events, and mortality from coronary heart disease compared with normal thyrotropin values (JAMA, 2019). In addition, thyrotropin values of 7.0 to 9.9 mU/L were associated with

increased risk of fatal stroke and mortality from coronary heart disease. The findings from the Journal of American Medical Association suggest that the severity of subclinical hypothyroidism is associated with greater cardiovascular risk.

The Journal of American Medical association suggest that treatment might be indicated for patients with subclinical hypothyroidism and serum thyrotropin levels of 10 mU/L or higher. Also, for young and middle-aged individuals with subclinical hypothyroidism and symptoms consistent with mild hypothyroidism, thyrotropin values of 7.0 to 9.9 mU/L (JAMA, 2019).

The Cardiovascular Health Study showed that SHT participants who were treated with levothyroxine had a 72% reduction in heart failure events (Jabbar et al, 2015). Thus, even mild hypothyroidism following acute myocardial infarction could be an important marker for poor outcome. Therefore, thyroxine in acute myocardial infarction needs further investigation and trials to prove its efficacy (Jabbar et al, 2015).

Monitoring and Duration of Treatment

The study done by Jabbar et al (2015) completed a 52-week study that kept their target TSH between 0.4 to 2.5 post AMI. After the study was complete, they sent data and recommendations to the patient's PCP in which it was the primary's discretion on whether to continue to treat their SHT. It was recommended to recheck the patients TSH after 6-weeks. Because increased age is a risk factor for hypothyroidism, hypertension and cardiovascular disease, its important to monitor TSH levels as it can be easily performed in the clinic setting (Udovcic et al, 2017).

The JAMA, Udovcic, Jabbar, Liu, Grias and Sowers, Stott all discuss the effects of hypothyroidism on the heart. All of which show data that supports the added cardiovascular

benefit of being euthyroid. There needs to be more studies conducted for treating SHT post AMI to really support the evidence. At this point there is no recommended time that patients with subclinical hypothyroidism should be on levothyroxine post AMI. The goal of preserving heart function which is to reduce workload on the heart by decreasing vascular resistance and increasing cardiac contractility. Being euthyroid will only be beneficial in reducing mortality as it relates to heart function (Udovcic et al, 2017).

Treating Subclinical Hypothyroidism

Overtreatment of SCH can cause complications and symptoms of thyrotoxicosis have been reported. Nervousness and anxiety were reported and some subjects "felt worse" following treatment in a placebo-controlled study (Stott et al, 2017). Tachyarrhythmias and angina pectoris were also reported. Low bone mass and fractures are also potential complications of treatment. Stott et al (2017) demonstrated the safety of thyroxine for the treatment of SCH, as no participants reported adverse effects, required dose reduction or withdrew from the studies (Stott et al, 2017).

For now, the treatment decision needs to be individualized. Treatment may be considered if: (a) symptoms are present; (b) there is a goiter; (c) there is risk of progression to OH; (d) there are risks of heart disease, particularly in patients younger than 70 years of age; or TSH levels exceed 10 mIU/L. Furthermore, SHT should be identified accurately (if possible) and treated adequately in pregnant women, lactating mothers, neonates and children. This is because unidentified and untreated SCH in these populations may lead to dire consequences (Stott et al, 2017).

Discussion

The evidence is still unclear as to whether subclinical hypothyroidism should be treated. The evidence is supportive of treating hypothyroidism as it relates to cardiac dysfunction. In the clinic setting it will be up to the primary care provider whether or not to treat SHT with hormone replacement. The information gathered from the American Thyroid Association, seven of the nine articles in the literature review suggest hormone replacement is beneficial to treat subclinical hypothyroidism as it relates to cardiac dysfunction. In the other two studies there was not enough data that suggested definitive treatment of subclinical hypothyroidism for each individual. The Journal of the American Medical Association recommended that treatment of subclinical hypothyroidism be patient based along with being symptomatic and under the age of 65, unless without evidence of CAD or recent MI (JAMA, 2019).

Learning Points

- Subclinical hypothyroidism will likely develop into overt hypothyroidism. Proper monitoring and subsequent thyroid replacement therapy should be implemented.
- The evidence is clear that thyroid hormone effects lipid levels. Treating those with symptomatic SHT and familial hyperlipidemia will help reduce mortality as it relates to cardiac dysfunction.
- Those 65 and older in need of thyroid hormone replacement should initiate levothyroxine at a low does and progress slowly. Especially with a history of CAD and MI.
- For those <65 years old with subclinical hypothyroidism and are symptomatic (weight gain, malaise, hypertension) would benefit from hormone replacement with levothyroxine.
- In the primary care setting for patients post AMI it would be prudent to check TSH levels 4-6 weeks to screen for overt and subclinical hypothyroidism.

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